Acute Myocardial Infarction Following Sildenafil Citrate (Viagra®) Intake in a Nitrate-Free Patient

AVITAL PORTER, M.D., AVIV MAGER, M.D., YOCHAI BIRNBAUM, M.D., BORIS STRASBERG, M.D., SAMUEL SCLAROVSKY, M.D.,
ELDAD RECHAVIA, M.D.

The Department of Cardiology, Rabin Medical Center, Beilinson Campus, Petah Tiqva, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Summary: Since its introduction to the market in March 1997, sildenafil acetate (Viagra®) has been prescribed to 1.7 million people. Sixteen men who were taking the drug have died, 7 of them during or soon after sexual activity. Most of these data have been derived from the media and not from the scientific literature. There is a general impression that cardiovascular complications of sildenafil occur mainly when the drug is taken concomitantly with nitrates. We describe a 65-year-old man with known coronary artery disease who had an acute myocardial infarction shortly after taking sildenafil and engaging in sexual activity. The patient had not been using nitrates. We suggest that the emotional arousal induced by Viagra, followed by the heavy physical exertion during sexual activity, triggers plaque rupture that leads to acute myocardial infarction.

Key words: acute myocardial infarction, physical exertion, stress, Viagra®, triggering

Introduction

Since sildenafil acetate (Viagra) was approved in March 1997, 1.7 million new prescriptions for the drug have been filled. Sixteen men who were taking the drug have died, 7 of

them during or soon after sexual activity.¹ At least 13 of the men were over age 50 years, and at least 3 were being treated with nitrates.² Although most of the data on sildenafil acetate have been derived from the media, there is more than anecdotal evidence linking the drug to cardiovascular complications. We describe a patient with known coronary artery disease, who had an acute myocardial infarction shortly after taking sildenafil and engaging in sexual activity.

Case Report

A 65-year-old man was admitted to the coronary care unit with an acute anterior wall myocardial infarction and primary ventricular fibrillation.

The patient had had ischemic heart disease and hypertension for the last 6 years. Two years before admission he underwent successful rotational atherectomy of a calcified lesion involving the proximal left anterior descending coronary artery (LAD). The patient was asymptomatic until 1.5 months before admission, then he began to complain of anginal pain on effort, during cold exposure, and during sexual activity. Repeated coronary angiography demonstrated a patent LAD and significant narrowing of the left circumflex artery. Treatment consisted of stent deployment with good angiographic results. Since then and until admission, the patient was asymptomatic, he walked daily for exercise, and did not take nitrates. One month before admission he started to take sildenafil, 50 mg at first and then 100 mg on four separate occasions, each intake followed by sexual activity. He had no anginal or other symptoms except for blue vision shortly after taking the pill. However, after the fifth intake (100 mg) 10 min after cessation of sexual activity, the patient experienced sharp chest pain. Admission electrocardiogram (ECG) in the emergency department showed ventricular fibrillation. The patient was defibrillated and transferred to the coronary care unit in stable hemodynamic condition; blood pressure was 120/70 mmHg, and there were no signs of congestion or mechanical complications. A second ECG in the coronary care unit revealed ST-segment elevation involving all precordial

Address for reprints:

Yochai Birnbaum, M.D.
Associate Director
Cardiac Intensive Care Unit
Department of Cardiology
Rabin Medical Center, Beilinson Campus
Petah Tiqva 49100, Israel

Received: October 8, 1998

Accepted with revision: February 9, 1999

leads. The patient received infusion of streptokinase (1.5 million units). During the infusion the patient underwent an episode of symptomatic sustained monomorphic ventricular tachycardia necessitating emergency electrical cardioversion. Because of persistent chest pain and ST-segment elevation, rescue angioplasty was performed. Coronary angiography demonstrated a discrete stenotic (40% diameter) lesion in the proximal LAD with TIMI flow grade 3 and a 50% instant narrowing of the left circumflex artery. The right coronary artery was slightly irregular. The ECG after angioplasty showed normalization of the ST-segment and Q-wave development in the precordial leads. The first 24 postprocedural hours were characterized by ventricular tachyarrhythmias treated with lidocaine and procainamide. Thereafter, no arrhythmia was noticed, but the patient complained of shortness of breath. This was attributed to moderate left ventricular dysfunction, mainly due to akinesis of the anteroapical wall. The rest of the hospital course was uneventful.

Discussion

Sildenafil acetate (Viagra) is a selective inhibitor of cyclic-GMP-specific phosphodiesterase type 5, the predominant isoenzyme metabolizing cyclic GMP in the corpus cavernosum, and is therefore used to enhance erectile response to sexual stimulation.³ Sildenafil has some vasodilator properties but no effect on heart rate. The drug has been shown to improve erectile function significantly,⁴ and a dose-response effect has been demonstrated after 6 months of therapy.⁵ It is generally well tolerated; the main adverse effects are headaches (14–30%), flushing (10–20%), dyspepsia (3–16%), and visual disturbances.^{4–6} The adverse cardiac effects reported to date include angina, syncope, tachycardia, palpitations, hypotension, and sudden death.⁷ Sildenafil has so far been implicated in 16 deaths, although no direct link was proved.

Suggested Mechanism of Sildenafil-Induced Myocardial Ischemia

Heavy physical exertion, sexual activity, and exposure to cold are well-known triggers of acute coronary events, especially in individuals who do not exercise regularly.^{8,9} In the MIOS study, 3% of the patients with myocardial infarction had engaged in sexual activity within the 24 h preceding infarction. They showed that sexual activity was associated with a relative risk of 2.1.⁹ Muller *et al.*¹⁰ assessed potential triggers of acute myocardial infarction in 1,774 patients and found that 3–9% of the patients engaged in sexual activity within the 24 h preceding the infarct. They showed that the relative risk of myocardial infarction in the 2 h after sexual activity did not differ between those with and without prior cardiac disease, that sexual activity contributed to the onset of infarction in only 0.9% of the cases, and that the risk was inversely related to the level and frequency of habitual physical

activity. The pathogenesis of acute coronary events following physical exertion includes coronary vasoconstriction (in patients with endothelial dysfunction), platelet activation, decreased fibrinolytic activity, increase in oxygen demand, and disruption of vulnerable plaque.

Our patient had an acute myocardial infarction shortly after taking sildenafil and engaging in sexual activity. The unusual strenuous exertion combined with the absence of a significant narrowing of the LAD following thrombolysis suggests that acute thrombosis or spasm was the underlying mechanism. Although a direct connection between the ischemic event and sildenafil intake can only be assumed at this point, it is not inconceivable that the drug contributed directly to the coronary event by enhancing transient thrombus formation or by leading the patient, who had known coronary artery disease, to participate in unusual strenuous physical activity. It is also noteworthy that our patient received the highest recommended dosage of the drug (100 mg), and that there might be a correlation between the dose of sildenafil and the occurrence of acute coronary events.

Whether sildenafil can act as the sole trigger of acute coronary events is a matter for further investigation. Although the drug offers a sufficiently sustained benefit to justify its therapeutic application in patients with sexual dysfunction, proper patient selection and education, especially regarding drug dosage and interactions, are warranted. Patients should be encouraged to exercise regularly and to control physical exertion during sexual activity.

References

1. FDA report, June 8, 1998 (Information taken from the Internet)
2. Dogar R: Just how safe is sex? *Newsweek* 1998;June 22:42
3. Boolel M, Allen MJ, Ballard SA, Gepi-Attee S, Muirhead GJ, Naylor AM, Osterloh IH, Gingell C: Sildenafil: An orally active type 5 cycGMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int J Impot Res* 1996;8:47–52
4. Boolel M, Gepi-Attee S, Gingell JC, Allen MJ: Sildenafil, a novel effective oral therapy for male erectile dysfunction. *Br J Urol* 1996;78:257–261
5. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA: Oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med* 1998;338:1397–1404
6. Morales A, Gingell C, Collins M, Wicker PA, Osterloh IH: Clinical safety of oral sildenafil citrate (Viagra™) in the treatment of erectile dysfunction. *Int J Impot Res* 1998;10:69–74
7. Pfizer Viagra®: Script No. 2275, Oct. 14, 1997, p. 24
8. Tofler GH, Stone PH, Maclure M, Edelman E, Davis VG, Robertson T: Analysis of possible triggers of acute myocardial infarction (the MILIS study). *Am J Cardiol* 1990;66:22–27
9. Mittelman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller J: Triggering of acute myocardial infarction by heavy physical exertion. *N Engl J Med* 1993;329:1677–1683
10. Muller JE, Mittelman A, Maclure M, Sherwood JB, Tofler GH: Triggering myocardial infarction by sexual activity. Low absolute risk and prevention by regular physical exertion. Determinants of myocardial infarction. *J Am Med Assoc* 1996;275:1405–1409